

Expert Opinion

1. Introduction
2. Pharmacology of ezetimibe, fenofibrate and the combination of ezetimibe plus fenofibrate
3. Clinical efficacy of ezetimibe, fenofibrate and the combination of ezetimibe plus fenofibrate
4. Conclusion
5. Expert opinion

For reprint orders, please contact:
Ben.Fisher@informa.com

informa
healthcare

Ezetimibe plus fenofibrate: a new combination therapy for the management of mixed hyperlipidaemia?

Michel Farnier

Point Médical, Rond Point de la Nation, 21000 Dijon, France

Mixed hyperlipidaemia is an important risk factor for the development of cardiovascular disease. The global management of mixed hyperlipidaemia is often more difficult than the treatment of pure hypercholesterolaemia in terms of goal attainments. Despite the significant clinical benefits provided by statins, many patients with mixed hyperlipidaemia do not achieve their recommended low-density and non-high-density lipoprotein cholesterol target goals with statin monotherapy. The combination of ezetimibe plus fenofibrate is a new alternative to improve the overall atherogenic lipid profile of patients with mixed hyperlipidaemia. However, the absence of comparative data with statin monotherapy and of long-term clinical studies suggests reservation of the combination of ezetimibe plus fenofibrate as a second-line therapy. Nevertheless, this combination therapy of ezetimibe plus fenofibrate seems particularly useful for patients with a poor response or intolerance to statin monotherapy.

Keywords: cardiovascular disease, ezetimibe, fenofibrate, HDL cholesterol, LDL cholesterol, mixed hyperlipidaemia, triglyceride

Expert Opin. Pharmacother. (2007) 8(9):1345-1352

1. Introduction

Mixed or combined hyperlipidaemia is a common metabolic disorder, occurring in ~ 30% of myocardial infarction (MI) survivors [1]. This disorder is characterised by both elevated low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG). The lipoprotein phenotype is usually associated with a decrease in high-density lipoprotein cholesterol (HDL-C) concentration, an elevated apolipoprotein B (ApoB) concentration and a preponderance of small, dense LDL particles. These small, dense LDL particles are thought to be more atherogenic because they are more easily oxidised, have a higher affinity for the extracellular matrix and a higher degree of retention in the arterial wall. Furthermore, small, dense LDL exhibits reduced binding to LDL receptors [2]. All the metabolic abnormalities of mixed hyperlipidaemia contribute to increased risk for cardiovascular disease (CVD). Mixed or combined hyperlipidaemia can be genetically determined. Moreover, mixed hyperlipidaemia is the most frequent lipid disorder found in patients with Type 2 diabetes and metabolic syndrome [3,4].

A large number of prospective clinical trials have demonstrated that the reduction of LDL-C is associated with significant reductions in risk for cardiovascular morbidity and mortality. Therefore, elevated LDL-C is identified as the primary target of lipid-lowering therapy by both US [3,5] and European [4,6] guidelines. Beyond lowering LDL-C, the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) introduced a secondary target of therapy, non-HDL-C, in patients with elevated triglycerides, to take into account the atherogenic potential associated with triglyceride-rich lipoproteins.

Statins are the most commonly used therapy to reduce LDL-C and non-HDL-C, and are effective in decreasing the risk of cardiovascular events. Although statins lower serum triglycerides to some extent, fibrates are more effective in decreasing TG and increasing HDL-C levels. The fibrates are less effective than statins regarding LDL-reduction and are also useful in lowering non-HDL-C levels. In addition, fibrates increase the buoyancy of the LDL particles and, therefore, might decrease the potential atherogenicity of these LDL particles. However, clinical trials using fibrates have reported mixed results. In subgroup analysis from The VAHIT (Veterans Affairs High density lipoprotein Intervention Trial) and the Bezafibrate Infarction Prevention Trial [7-10], the benefit of fibrates mainly appear for patients with high TG and low HDL-C lipid profiles and/or with Type 2 diabetes and metabolic syndrome. At the opposite end, the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study has not been able to show a robust effect of fenofibrate in reducing cardiovascular risk in a specific population of Type 2 diabetic patients [11]. However, the population from FIELD was not characterised by elevated TG and low HDL-C at baseline and the effect of fenofibrate alone on lipid parameters was relatively modest. The FIELD results clearly suggest that the future of fenofibrate can be mainly in combination therapies with other classes of lipid-lowering drugs.

The NCEP ATP III guidelines [3,5] recommend combining drug therapies to achieve the lipid goals for patients with mixed hyperlipidaemia. The combination of statins with fibrates is, therefore, a powerful strategy for mixed hyperlipidaemia [12], due to complementary mechanisms of action and correction of multiple lipoprotein abnormalities. However, when fibrates are used in combination with statins, attention must be paid to the risk for myositis and rhabdomyolysis [13], even if this risk is less with fenofibrate compared to gemfibrozil [14,15]. Moreover, some patients with mixed hyperlipidaemia are intolerant or non-responsive to statin therapy, and there is a need for other alternative combined therapies. The combination of ezetimibe plus fenofibrate can be one of the new alternatives for the management of mixed hyperlipidaemia.

2. Pharmacology of ezetimibe, fenofibrate and the combination of ezetimibe plus fenofibrate

2.1 Ezetimibe

The concentration of plasma cholesterol is maintained by biosynthesis through the endogenous pathway and by absorption of dietary and biliary cholesterol through the exogenous pathway [16]. Ezetimibe is the first of a class of selective cholesterol absorption inhibitors and is a synthetic 2-azetidinone, whose chemical name is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone.

Originally developed as acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors, it soon became clear that

2-azetidinones do not inhibit ACAT2 in a relevant manner, but do block the intestinal absorption of cholesterol. Ezetimibe effectively inhibits the intestinal absorption of cholesterol and plant sterols without affecting absorption of triglycerides, fatty acids, bile acids or fat-soluble vitamins [17]. Thus, ezetimibe differs from orlistat, which inhibits pancreatic lipase, and from bile acid resins, which sequester bile acids. The exact mechanism of action is not yet fully elucidated. However, there is now evidence to show that ezetimibe inhibits at least two different types of sterol transporters in the mouse small intestine [18]. The first is the Niemann-Pick C1-like 1 protein, which is a critical mediator of cholesterol and phytosterol absorption, and an essential component of the ezetimibe-sensitive pathway [19-21]. The second potential target of ezetimibe is a protein complex of annexin-2 and caveolin-1 that also seems to be involved in intracellular sterol trafficking [22]. On reaching the duodenum, ezetimibe is rapidly absorbed from the intestinal lumen and undergoes extensive glucuronidation in the intestinal wall [17,23,24]. Once glucuronidated, ezetimibe circulates enterohepatically, resulting in repeated delivery to the site of action in the intestine and thus limiting the peripheral exposure [17]. This recirculation may explain the long half-life (~ 22h) of ezetimibe, which allows for once-daily dosing of the drug. Ezetimibe localises in the intestinal wall, mainly as the glucuronide, which is a more potent inhibitor of cholesterol absorption than ezetimibe [25]. Ezetimibe is mainly excreted in the faeces (as the parent drug), with a small proportion in the urine (as glucuronide) [26].

There was no clinically significant effect of food on the oral bioavailability of ezetimibe [26]. Ezetimibe is unlikely to cause drug interactions with common CYP450 substrates [23,26]. No changes in the pharmacokinetics of statins, warfarin, digoxin, ethinyl estradiol or glipizide were observed when these agents were administered with ezetimibe. Coadministration of colestyramine reduced the AUC of ezetimibe by $\leq 80\%$. Ciclosporin increases the bioavailability of ezetimibe by approximately four-fold. Due to the unknown effects on the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ezetimibe is not recommended in these patients [23]. The mean AUC for total ezetimibe is increased ~ 1.5-fold in severe renal disease (creatinine clearance ≤ 30 ml/min/1.73 m²). However, non-adjustments are presently recommended for patients with renal insufficiency.

A study conducted in hypercholesterolaemic subjects confirmed the mode of action of ezetimibe as an inhibitor of cholesterol absorption in humans [27]. This double-blind, placebo-controlled, crossover study in 18 men with mild-to-moderate hypercholesterolaemia evaluated the effects of 2 weeks of treatment with ezetimibe 10 mg on intestinal absorption. Ezetimibe decreased fractional cholesterol absorption by 54% and LDL-C levels by 20% compared with placebo. This was associated with a compensatory increase of cholesterol hepatic synthesis, as reflected by an increase in the

lathosterol:cholesterol ratio. Ezetimibe also reduced plasma concentrations of campesterol and sitosterol by 48 and 41%, respectively [27].

2.2 Fenofibrate

Fibrates are a class of lipid-lowering drugs used in the treatment of patients with hypertriglyceridaemia, mixed hyperlipidaemia, metabolic syndrome and/or diabetic dyslipidaemia [28,29]. The mechanism of action of fibrates on lipid and lipoprotein metabolism is now well established [30,31] and fibrates also exhibit numerous metabolic effects beyond their lipid-modifying properties [31]. Among fibrates, fenofibrate has been available since 1975 and the pharmacological properties of fenofibrate have been reported in many reviews [32-34].

Fenofibrate is the isopropyl ester of 2-[4-(4-chlorobenzoyl)-phenoxy]-2-methyl propanoic acid and is a prodrug that is converted in the pharmacologically active metabolite fenofibric acid. After the original 300 mg standard formulation, several formulations of the drug have been developed to improve its bioavailability: a capsule formulation of micronised fenofibrate available in 67, 200 and 267 mg doses, a microcoated tablet formulation available in a 160 mg dose and a new nanoparticle tablet formulation available in a 145 mg dose.

Recent studies have shown that the molecular pharmacological effects of fenofibrate are mediated by its activation of the PPAR- α . Activated PPAR- α stimulates the expression of genes encoding various enzymes that regulate fatty acid and lipoprotein metabolism [29,31,34]. Fenofibrate stimulated different steps in fatty acid oxidative metabolism in different organs, particularly in the liver. This promotion of the β -oxidation of fatty acids reduced the availability of fatty acids for very-low-density lipoprotein (VLDL) synthesis and secretion. Another key mechanism for the triglyceride-lowering effects of fenofibrate is the promotion of intravascular lipolysis. Fenofibrate increased the expression of lipoprotein lipase and decreased ApoC-III expression in the liver. In fact, fenofibrate altered both the synthesis and the catabolism of the triglyceride-rich lipoproteins [30,34]. Moreover, fenofibrate treatment reduced the proportion of small, dense LDL, with the formation of larger, less dense LDL particles with a higher affinity for the LDL receptor and thus catabolised more rapidly [35]. PPAR- α activation with fenofibrate also increased ApoA-I and ApoA-II synthesis and decreased the cholesteryl ester transfer protein-mediated transfer of cholesterol from HDL to VLDL. All these effects contribute to the increase of plasma HDL-C concentrations [36,37].

Fenofibrate also has numerous pleiotropic effects mediated by PPAR- α activation [30,31], such as effects on fibrinogen, plasminogen activator inhibitor or vascular inflammation [34].

Fenofibrate is rapidly hydrolysed to its active metabolite, fenofibric acid. The half-life of fenofibric acid is 20 h, allowing for once-daily administration. Fenofibrate is mainly excreted in the urine, as fenofibric acid and fenofibric acid glucuronide [34]. The clearance of fenofibrate

is greatly reduced in patients with renal dysfunction and dose reduction is recommended in patients with renal impairment [34].

Fenofibrate has a low potential for drug interactions, with the exception of its interaction with ciclosporin, in which case, a potential increase of the nephrotoxicity of ciclosporin occurs in patients receiving fenofibrate [34]. Concomitant administration of fenofibrate has no clinically significant effect on the pharmacokinetics of simvastatin, rosuvastatin or atorvastatin, and only modest effects on the exposure of pravastatin. The pharmacokinetics of fenofibrate are not significantly modified by the concomitant administration of statins [34]. No pharmacokinetic studies of fenofibrate are available in patients with hepatic impairment. Fenofibrate has also been shown to potentiate the effect of coumarin-type anticoagulants.

2.3 The combination of ezetimibe plus fenofibrate

The pharmacodynamic and pharmacokinetic interaction between ezetimibe and fenofibrate has been evaluated in healthy subjects with primary hypercholesterolaemia, in a 2-week, placebo-controlled, parallel-group study comparing ezetimibe-fenofibrate combination therapy, ezetimibe alone, fenofibrate alone and placebo [38]; ezetimibe did not significantly affect the pharmacokinetics of fenofibrate. The concomitant administration of fenofibrate 200 mg micronised and ezetimibe 10 mg resulted in a significant (~ 50%) increase in steady-state total ezetimibe exposure. The mean C_{max} and the AUC of total ezetimibe were significantly increased by ~ 64 and 48%, respectively. However, this increase in total ezetimibe exposure was not considered to be clinically significant, considering the flat dose-response of ezetimibe for LDL-C decrease and safety. Doubling the dose of ezetimibe from 10 to 20 mg/day only induced an additional mean 1.5% reduction in LDL-C [39]. In the same dose-ranging study, doses between 10 and 40 mg/day had a similar incidence of adverse events [39].

3. Clinical efficacy of ezetimibe, fenofibrate and the combination of ezetimibe plus fenofibrate

3.1 Ezetimibe

The efficacy and safety of ezetimibe administered as single agent therapy at a dose of 10 mg/day in patients with primary hypercholesterolaemia have been assessed in four large-scale, placebo-controlled, double-blind studies. Pooled results of the two Phase II studies showed that, compared with placebo, ezetimibe 10 mg significantly reduced LDL-C levels by 18.5% and increased HDL-C levels by 3.5% [40]. Similarly, in the two Phase III studies, ezetimibe 10 mg significantly reduced directly measured LDL-C from baseline by 16.9 [41] and 17.7% [42] compared with increases of 0.4 and 0.8%, respectively, with placebo. In addition, ezetimibe significantly improved HDL-C (~ 1%) and ApoB in both studies. The

reduction of triglycerides compared with placebo was significant only in one study [41]. In all the Phase II and III studies, ezetimibe monotherapy was well tolerated, with an adverse event profile of ezetimibe similar to that in the placebo group. There are no end point trials evaluating the benefit of ezetimibe monotherapy to reduce risk for cardiovascular morbidity and mortality.

3.2 Fenofibrate

The potential of monotherapy with fenofibrate in the treatment of patients with primary dyslipidaemia has been well established in numerous, placebo-controlled and comparative trials [32-34]. Fenofibrate therapy was consistently associated with a substantial decrease of serum triglycerides by 20 – 50% and an increase in HDL-C levels by 10 – 20%, as well as an increase in ApoA-I. The effect of fenofibrate on LDL-C levels was mainly dependent of the type of dyslipidaemia; in patients with mixed dyslipidaemia and modest hypertriglyceridemia, fenofibrate generally produced less reductions in LDL-C than in primary hypercholesterolemia [32]. Patients with severe hypertriglyceridaemia and low levels of LDL-C may raise their LDL-C levels during fenofibrate treatment, possibly as a result of an accelerated catabolism of triglyceride-rich lipoproteins, leading to an increased LDL conversion.

Fenofibrate also has numerous pleiotropic effects, such as anti-inflammatory, antioxidant and antithrombotic effects [29,34]. In patients with dyslipidaemia, fenofibrate therapy reduced plasma fibrinogen, C-reactive protein levels, proinflammatory cytokines, IL-6, TNF- α and monocyte chemoattractant protein-1 [34]. Fenofibrate also improved endothelial dysfunction [43,44]. Among fibrates, only fenofibrate significantly reduced uric acid levels [34,45]. At the opposite end, fenofibrate therapy induced two potential deleterious effects: an increase in creatinine levels [34,46] and a significant elevation in homocysteine levels [34,47].

The potential cardiovascular protection of fenofibrate therapy has only been evaluated in diabetic patients. In the DAIS (Diabetes Atherosclerosis Intervention Study) [48], fenofibrate slowed the angiographic progression of coronary atherosclerosis; the progression of focal coronary atheroma was 40% less in the fenofibrate group compared with placebo, without significant effect on diffuse atheroma.

Additionally, there was a 23% reduction in the rate of cardiovascular events, but this reduction did not reach a statistically significant level, possibly due to the small number of patients enrolled in the trial. These effects seemed to be explained not only by the changes in HDL-C, LDL-C and triglycerides levels, but also by the significant increase in LDL particle size observed in the fenofibrate group [49]. Interestingly, the increase of homocysteine does not alter the beneficial effect of fenofibrate in DAIS [50].

The ability of fenofibrate to reduce clinical outcomes in Type 2 diabetes has been tested in a large population of 9795 patients with (22%) and without (78%) previous CVD [11]. In the

FIELD study, fenofibrate therapy was associated with a nonsignificant 11% reduction in the primary end point (coronary heart disease [CHD] death and non-fatal MI), corresponding to a significant 24% reduction in non-fatal MI and a nonsignificant 19% increase in CHD mortality. The incidence of total cardiovascular events was significantly less in the fenofibrate group, but the beneficial effect only occurred in patients with no previous CVD. Some explanations can be proposed to explain the disappointing results of FIELD; it has been suggested that the higher rate of statin use in the placebo group may play a role, but even after adjustment for statin therapy, reduction of CHD events remains less important than the effect observed in diabetic patients from statin trials, such as the Heart Protection Study and the Collaborative Atorvastatin Diabetes Study [51,52]. The poor effect of fenofibrate in reducing CVD events, more particularly in secondary prevention, could also be explained by the significant increase of homocysteine levels. It has been shown that gemfibrozil increased plasma homocysteine less than fenofibrate [47,53], and this difference could explain the better clinical benefit of gemfibrozil in the VAHIT [7,8] and Helsinki Heart Study [54]. Another hypothesis to explain the FIELD results is the modest effects of fenofibrate on lipid parameters. In particular, the effect on HDL-C decreased over time in FIELD (+ 5% after 4 months, + 1.2% at the end of the study). In FIELD, the mean HDL-C at baseline was normal, higher than in DAIS, and the effect of a fibrate on HDL-C levels depends mainly on patients' lipid profiles. The declining effect of fenofibrate on HDL-C over time could also be due to the fact that elevated homocysteine reduces the ApoA-I expression in mice and humans [55].

In diabetic populations, in terms of effects on microvascular disease, fenofibrate reduced the progression of albuminuria in FIELD and DAIS trials [11,56] and the need of laser treatment for retinopathy [11].

In the treatment of dyslipidaemia, fenofibrate was generally well tolerated, with few side effects [101,102]. The most common side effects were gastrointestinal disturbances, liver function test abnormalities and increased creatine phosphokinase. Fenofibrate also increased plasma creatinine levels by an unclear mechanism [34]. In patients with Type 2 diabetes who participated in the FIELD trial, a slight but significant increase in pancreatitis (0.8 in fenofibrate group versus 0.5% in placebo group) and pulmonary embolism (1.1 versus 0.7%), and a nonsignificant increase in deep vein thrombosis (1.4 versus 1.0%) were observed. The excess of pancreatitis may be due to the increased lithogenicity of bile. The increased risk of venous thrombotic events may be related to the increased homocysteine level, a risk factor for thrombosis [57]. Overall, in FIELD, rhabdomyolysis only occurred in three fenofibrate recipients and one placebo recipient, and all cases were fully resolved.

3.3 The combination of ezetimibe plus fenofibrate

The efficacy of ezetimibe plus fenofibrate combination therapy has been evaluated in a specific population of patients

with mixed hyperlipidaemia [58,59]. Indeed, due to the complementary biological efficacy of these two drugs, mixed hyperlipidaemia appears the best choice for this new combination therapy. In this multi-centre trial, the efficacy and safety of ezetimibe coadministered with fenofibrate was compared with that of ezetimibe alone, fenofibrate alone and placebo during 12 weeks [58]. A total of 625 patients with serum triglycerides between 200 and 500 mg/dl, LDL-C between 130 and 220 mg/dl (100 – 180 mg/dl in patients with diabetes [16%]) were randomised to receive one of the four daily treatments: placebo, ezetimibe 10 mg, fenofibrate 160 mg and ezetimibe 10 mg + fenofibrate 160 mg. The coadministration therapy reduced LDL-C by 20.4%, non-HDL-C by 30.4%, TG by 44.0% and increased HDL-C by 19.0%. The change in LDL-C was influenced by baseline TG levels; greater LDL-C lowering was noted in all active treatments in patients with TG \leq 3.1 mmol/l (median). At baseline, \geq 70% of patients in each treatment group had an atherogenic LDL size pattern B (preponderance of small, dense LDL particles) [2].

After treatment, a greater proportion of patients receiving ezetimibe plus fenofibrate (64%) and fenofibrate alone (62%) treatments shifted from a more atherogenic LDL size pattern to a larger, more buoyant and less atherogenic size pattern. Depending on the study variable, the effects of the combination of ezetimibe plus fenofibrate were either additive (LDL-C, total cholesterol, non-HDL-C and ApoB) or fenofibrate-dependent (TG, HDL-C, ApoA-I, high-sensitivity C-reactive protein, fibrinogen and LDL size pattern shift). Finally, LDL-C and non-HDL-C goal attainment was greater with coadministration than with either single treatment: \sim 60% of patients treated with ezetimibe plus fenofibrate reached LDL-C and non-HDL-C targets.

After completing the 12-week, randomised, double-blind base study, 576 patients entered into a 48-week, double-blind, extension study, during which they received fenofibrate ($n = 236$) or ezetimibe plus fenofibrate ($n = 340$) [59]. Improvements from baseline in LDL-C (-22.0 versus -8.6%), non-HDL-C (-31.6 versus -19.4%), ApoB (-25.2 versus -16.2%), TG (-46.0 versus -41.8%) and HDL-C (20.9 versus 17.8%) levels were significantly greater with ezetimibe-fenofibrate combination therapy than with fenofibrate alone.

The combination of ezetimibe plus fenofibrate was well tolerated during both the base study [58] and the extension study [59]. In the base study, the proportion of patients with elevations in liver function tests or serum creatinine was similar between the combination group and the fenofibrate group. It has been reported that fenofibrate increases cholesterol excretion into bile [101,102], which may lead to cholelithiasis, and ezetimibe has inconsistent effects on biliary cholesterol in animal models [103], but without evidence of an increased risk of gallstones in patients with primary hypercholesterolaemia [40-42]. In the base study, one patient receiving the combination of ezetimibe plus fenofibrate was discontinued after being diagnosed with cholelithiasis and

subsequent cholecystectomy. In the extension study, the proportion of patients with planned or performed cholecystectomy was not significantly different between treatments. However, this study was not designed to assess this infrequent biliary adverse event.

Finally, there are no data on the rates of cholesterol absorption and cholesterol hepatic synthesis induced by the combination of ezetimibe plus fenofibrate.

4. Conclusion

The combination of ezetimibe with fenofibrate is an additional alternative approach to the treatment of patients with mixed hyperlipidaemia. This combination therapy seems to be particularly useful in patients who have a poor response to, or are intolerant to, statin therapy.

5. Expert opinion

Numerous clinical end point trials [60] have firmly established the efficacy of statins to reduce cardiovascular events. Therefore, the use of statins has become the cornerstone of drug therapy in reducing the concentration of LDL-C and thereby the risk of CVD. Statins are indicated as first-line therapy for patients with primary hypercholesterolaemia and mixed hyperlipidaemia. Despite the benefits of statin therapy, the residual risk observed in clinical trials can partly be explained by the fact that abnormalities in triglyceride-rich lipoproteins and HDL contribute to the risk of CVD. Although statins are the drug of first choice in patients with mixed hyperlipidaemia, statin therapy may be limited by the failure to reach non-HDL-C goals and by intolerance or poor response in monotherapy. Fenofibrate is a second choice treatment for these patients, but the benefits of fenofibrate on cardiovascular outcomes observed in patients with Type 2 diabetes are less than those observed with statins. This lack of benefit with fenofibrate can be a reflection of the poor effect of fenofibrate monotherapy on lipid parameters. The combination of ezetimibe plus fenofibrate offers a new strategy for patients with mixed hyperlipidaemia. The complementary effects of ezetimibe and fenofibrate improve the overall atherogenic lipid profile observed for these patients with decreases of LDL-C (-20%), non-HDL-C (-30%), ApoB (-26%) and TG (-44%) and increase of HDL-C (+19%). Moreover, a large proportion of patients with mixed hyperlipidaemia can simultaneously reach LDL-C and non-HDL-C goals with this combination therapy. Even if no direct comparative data with statin monotherapy are available, the global improvement of lipid profiles suggests that the combination of ezetimibe plus fenofibrate could be an alternative of statin monotherapy.

The limitation of the use of this combination of ezetimibe plus fenofibrate is mainly due to the remaining questions regarding the long-term clinical benefit of fenofibrate therapy and the long-term safety profile of the ezetimibe plus

fenofibrate treatment. Until then, this combination seems to be reserved as a second-line therapy. Nevertheless, the ezetimibe plus fenofibrate combination therapy offers an important treatment alternative to patients with mixed hyperlipidaemia who respond inadequately or are intolerant to statin therapy.

Declaration of interest

M Farnier has previously received financial support from Merck. This article was independently commissioned and no fee has been received for preparation of the manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

- DURRINGTON P: Dyslipidaemia. *Lancet* (2003) 362:717-731.
- PACKARD CJ: Small dense low-density lipoprotein and its role as an independent predictor of cardiovascular disease. *Curr. Opin. Lipidol.* (2006) 17:412-417.
- Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* (2001) 285:2486-2497.
- THE TASK FORCE ON DIABETES AND CARDIOVASCULAR DISEASES OF THE EUROPEAN SOCIETY OF CARDIOLOGY (ESC) AND THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (EASD): Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. *Eur. Heart J.* (2007) 28:88-136.
- GRUNDY SM, CLEEMAN JJ, MERZ CNB *et al.* FOR THE COORDINATING COMMITTEE OF THE NATIONAL CHOLESTEROL EDUCATION PROGRAM: Implications or recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* (2004) 110:227-239.
- DE BACKER G, AMBROSIONI E, BORCH-JONSEN K *et al.*: European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur. Heart J.* (2003) 24:1601-1610.
- ROBINS SJ, COLLINS D, WITTES JT *et al.* FOR THE VA-HIT STUDY GROUP: Relation of gemfibrozil treatment and lipid levels with major coronary events - VA-HIT: a randomized controlled trial. *JAMA* (2001) 285(12):1585-1591.
- RUBINS HB, ROBINS SJ, COLLINS D *et al.*: Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch. Intern. Med.* (2002) 162:2597-2604.
- TENENBAUM A, MOTRO M, FISMAN EZ *et al.*: Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch. Intern. Med.* (2005) 165:1154-1160.
- THE BIP STUDY GROUP: Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) study. *Circulation* (2000) 102:21-27.
- THE FIELD STUDY INVESTIGATORS: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD Study): randomised controlled trial. *Lancet* (2005) 366(9500):1849-1861.
- FARNIER M: Combined therapy with a HMG-CoA reductase inhibitor and a fibric acid derivative: a critical review of potential benefits and drawbacks. *Am. J. Cardiovasc. Drugs* (2003); 3(3):169-178.
- CORSINI A, BELLOSTA S, DAVIDSON MH: Pharmacokinetic interactions between statins and fibrates. *Am. J. Cardiol.* (2005) 96(Suppl.): 44K-49K.
- ALSHEIKH-ALI AA, KUVIN JT, KARAS RH: Risk of adverse events with fibrates. *Am. J. Cardiol.* (2004) 94:935-938.
- JONES PH, DAVIDSON MH: Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any statin. *Am. J. Cardiol.* (2005) 95:120-122.
- SHEPHERD J: The role of the exogenous pathway in hypercholesterolemia. *Eur. Heart J.* (2001) 3(Suppl. E): E2-E5.
- CATAPANO AL: Ezetimibe: a selective inhibitor of cholesterol absorption. *Eur. Heart J.* (2001) 3(Suppl.): E6-E10.
- SUDHOP T, LUTJOHANN D, VON BERGMANN K: Sterol transporters: targets of natural sterols and new lipid lowering drugs. *Pharmacol. Ther.* (2005) 105:333-341.
- Excellent review on the intestinal transport and regulation of sterols.
- ALTMANN SW, DAVIS Jr HR, ZHU L *et al.*: Niemann-Pick C1-Like 1 protein is critical for intestinal cholesterol absorption. *Science* (2004) 303:1201-1204.
- GARCIA-CALVO M, LISNOCK JM, BULL HG *et al.*: The target of ezetimibe is Niemann-Pick C1-Like1 (NPC1L1). *Proc. Natl. Acad. Sci. USA* (2005) 102(23):8132-8137.
- DAVIES JP, IOANNOU YA: The role of the Niemann-Pick C1-Like1 protein in the subcellular transport of multiple lipids and their homeostasis. *Curr. Opin. Lipidol.* (2006) 7:221-226.
- SMART EJ, De ROSE RA, FARBER SA: Annexin 2-caveolin 1 complex is a target of ezetimibe and regulates intestinal cholesterol transport. *Proc. Natl. Acad. Sci. USA* (2004) 101(10):3450-3455.
- JEU LA, CHENG JWM: Pharmacology and therapeutics of ezetimibe (SCH 58235), a cholesterol-absorption inhibitor. *Clin. Ther.* (2003) 25(9):2352-2387.
- GHOSAL A, HAPANGAMA N, YUAN Y *et al.*: Identification of human UDP-glucuronosyltransferase enzyme(s) responsible for the glucuronidation of ezetimibe (Zetia). *Drug Metab. Dispos.* (2004) 32(3):314-320.

25. VAN HECK M, FARLEY C, COMPTON DS *et al.*: Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663. *Br. J. Pharmacol.* (2000) 129:1748-1754.
26. DARKES MJM, POOLE RM, GOA KL: Ezetimibe. *Am. J. Cardiovasc. Drugs* (2003) 3(1):67-76.
27. SUDHOP T, LUTJOHANN D, KODAL A *et al.*: Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* (2002) 106:1943-1948.
28. FRUCHART JC, BREWER HB, LEITERSDORF E: Consensus for the use of fibrates in the treatment of dyslipoproteinemia and coronary heart disease. *Am. J. Cardiol.* (1998) 81:912-917.
29. FRUCHART JC, STAELS B, DURIEZ P: The role of fibric acids in atherosclerosis. *Curr. Atheroscl. Rep.* (2001) 3:83-92.
30. STAELS B, DALLONGEVILLE J, AUWERX J, SCHOONJANS K, LEITERSDORF E, FRUCHART JC: Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* (1998) 98:2088-2093.
31. FAZIO S, LINTON MF: The role of fibrates in managing hyperlipidemia: mechanisms of action and clinical efficacy. *Curr. Atheroscl. Rep.* (2004) 6:148-157.
32. ADKINS JC, FAULDS D: Micronised fenofibrate. A review of its pharmacodynamic properties and clinical efficacy in the management of dyslipidaemia. *Drugs* (1997) 54(4):615-633.
33. KEATING GM, ORMROD D: Micronised fenofibrate. An updated review of its clinical efficacy in the management of dyslipidaemia. *Drugs* (2002) 62(13):1909-1944.
34. KEATING GM, CROOM KF: Fenofibrate. A review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellitus. *Drugs* (2007) 67(1):121-153.
- Recent review on the effects of fenofibrate in patients with dyslipidaemia, metabolic syndrome and diabetes.
35. CHAPMAN MJ: Fibrates: therapeutic review. *Br. J. Diabetes Vasc. Dis.* (2006) 6(1):11-18.
36. GUERIN M, BRUCKERT E, DOLPHIN PJ *et al.*: Fenofibrate reduces plasma cholesteryl ester transfer from HDL to VLDL and normalizes the atherogenic dense LDL profile in combined hyperlipidemia. *Arterioscler. Thromb. Vasc. Biol.* (1996) 16(6):763-772.
37. FRUCHART JC, DURIEZ P: Mode of action of fibrates in the regulation of triglycerides and HDL-cholesterol metabolism. *Drugs Today* (2006) 42(1):39-64.
38. KOSOGLOU T, STATKEVICH P, FRUCHART JC *et al.*: Pharmacodynamic and pharmacokinetic interaction between fenofibrate and ezetimibe. *Curr. Med. Res. Opin.* (2004) 20(8):1197-1207.
39. STEIN E: Results of Phase I/II clinical trials with ezetimibe, a novel selective cholesterol absorption inhibitor. *Eur. Heart J.* (2001) 3(Suppl. E): E11-E16.
40. DUJOVNE CA, ETTINGER MP, McNEER JF *et al.* FOR THE EZETIMIBE STUDY GROUP: Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am. J. Cardiol.* (2002) 90:1092-1097.
41. KNOPP RH, GITTER H, TRUITT T *et al.* FOR THE EZETIMIBE STUDY GROUP: Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. *Eur. Heart J.* (2003) 24:729-741.
42. BAYS HE, MOORE PB, DREHOBL MA *et al.* FOR THE EZETIMIBE STUDY GROUP: Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. *Clin. Ther.* (2001) 23(8):1209-1230.
43. KOH KK, HAN SH, QUON MJ *et al.*: Beneficial effects of fenofibrate to improve endothelial dysfunction and raise adipopectin levels in patients with primary hypertriglyceridemia. *Diabetes Care* (2005) 28(6):1419-1424.
44. CAPELL WH, DeSOUZA CA, POIRIER P *et al.*: Short-term triglyceride lowering with fenofibrate improves vasodilator function in subjects with hypertriglyceridemia. *Arterioscler. Thromb. Vasc. Biol.* (2003) 23:307-313.
45. LIAMIS G, BAIRAKTARI ET, ELISAF MS: Effect of fenofibrate on serum uric acid levels. *Am. J. Kidney Dis.* (1999) 34: 594.
46. TSIMICHODIMOS V, BAIRAKTARI E, ELISAF M: Fibrate-induced increase in serum urea and creatinine levels. *Nephrol. Dial. Transplant* (2002) 17(4):682.
47. DIERKES J, WESTPHAL S, LULEY C: Fenofibrate-induced hyperhomocysteinaemia. Clinical implications and management. *Drug Saf.* (2003) 26(2):81-91.
48. DIABETES ATHEROSCLEROSIS INTERVENTION STUDY INVESTIGATORS: Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study. *Lancet* (2001) 357(9260):905-910.
49. VAKKILAINEN J, STEINER G, ANSQUER JC *et al.*: Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: the Diabetes Atherosclerosis Intervention Study (DAIS). *Circulation* (2003) 107:1733-1737.
50. GENEST J, FROHLICH J, STEINER G: Effect of fenofibrate-mediated increase in plasma homocysteine on the progression of coronary artery disease in type 2 diabetes mellitus. *Am. J. Cardiol.* (2004) 93(7):848-853.
51. HEART PROTECTION STUDY COLLABORATIVE GROUP: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* (2003) 361:2005-2016.
52. COLHOUN HM, BETTERIDGE DJ, DURRINGTON PN *et al.* ON BEHALF OF THE CARDS INVESTIGATORS: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* (2004) 364:685-696.
53. SYVANNE M, WHITTALL RA, TURPEINEN U *et al.*: Serum homocysteine concentrations, gemfibrozil treatment, and progression of coronary atherosclerosis. *Atherosclerosis* (2004) 172:267-272.
54. FRICK MH, ELO O, HAAPA K *et al.*: Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men

- with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N. Engl. J. Med.* (1987) 317:1237-1245.
55. MIKAEL LG, GENEST J Jr, ROZEN R: Elevated homocysteine reduces apolipoprotein A-I expression in hyperhomocysteinemic mice and in males with coronary artery disease. *Circ. Res.* (2006) 98:564-571.
 56. ANSQUER JC, FOUCHER C, RATTIER S, TASKINEN MR, STEINER G, DAIS INVESTIGATORS: Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). *Am. J. Kidney Dis.* (2005) 45(3):485-493.
 57. UNDAS A, BROZEK J, SZCZEKLIK A: Homocysteine and thrombosis: from basic science to clinical evidence. *Thromb. Haemost.* (2005) 94:907-915.
 58. FARNIER M, FREEMAN MW, MacDONELL G *et al.*: Efficacy and safety of the co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidemia. *Eur. Heart J.* (2005) 26:897-905.
 59. McKENNEY JM, FARNIER M, LO KW *et al.*: Safety and efficacy of long-term co-administration of fenofibrate and ezetimibe in patients with mixed hyperlipidemia. *J. Am. Coll. Cardiol.* (2006) 47(8):1584-1587.
 60. CHOLESTEROL TREATMENT TRIALIST'S (CTT) COLLABORATORS: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90056 participants in 14 randomised trials of statins. *Lancet* (2005) 366:1267-1278.

Websites

101. <http://emc.medicines.org.uk>
Fournier Pharmaceuticals Ltd. Supralip® 160mg: summary of product characteristics. Accessed 6 April 2006.
102. <http://tricortablets.com>
Abbott Laboratories. Tricor® 48mg and 145mg (fenofibrate tablets): prescribing information. Accessed 3 April 2006.
103. <http://www.fda.gov>
Merck/Schering-Plough Pharmaceuticals. Zetia® (ezetimibe) tablets: prescribing information. Accessed 10 May 2006.

Affiliation

Michel Farnier PhD, MD
Point Médical, Rond Point de la Nation,
21000 Dijon, France
Tel: +33 380 703 813;
Fax: +33 380 703 894;
E-mail: michelfarnier@nerim.net